APPENDIX D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF
Nabil HANNA *et al.*
Application Serial No. 09/612,914
Filed: July 10, 2000
Title: RECOMBINANT ANTI-CD4 ANTIBODIES FOR HUMAN THERAPY

Group Art Unit: 1642
Examiner: Christopher Yaen

April 25, 2005

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SUPPLEMENTAL PRELIMINARY AMENDMENT
IN RESPONSE TO THE NOTICE OF NON-COMPLIANT
AMENDMENT DATED DECEMBER 9, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is submitted in response to the Notice of Non-Compliant Amendment dated December 9, 2003, and is filed with a petition for withdrawal of the holding of abandonment stated in the Notice of Abandonment mailed February 23, 2005.

In place of the preliminary amendment filed on November 12, 2003, in reply to the final office action mailed on March 11, 2003, please enter this preliminary amendment for consideration in continuing examination. This preliminary amendment is responsive to the final official action dated March 11, 2003. The preliminary amendment that was filed on November 12, 200, was timely filed within two months of the filing of the Notice of Appeal on September 11, 2003, on the day following a national holiday (Veterans' Day).

No fee is believed to be due; however, authorization is hereby made to charge any additional fees that may be required by this submission to Deposit Account No. 033975.

I. AMENDMENT

IN THE SPECIFICATION:

Please replace the paragraph beginning at page 1, line 3, with the following rewritten paragraph:

-- This application is a continuation of Application No. 08/523,894, filed September 6, 1995, and issued as U.S. Pat. No. 6,136,310, which is a continuation-in-part of Application No. 08/476,237, filed June 7, 1995, and issued as U.S. Pat. No. 5,756,096, which is a continuation-in-part of Application No. 08/379,072, filed ~~April 17~~ January 25, 1995, and issued as U.S. Pat. No. 5,658,570, which is a continuation of Application No. 07/912,292, filed July 10, 1992 (abandoned), which is a continuation-in-part of Application No. 07/856,281, filed March. 23, 1992 (abandoned), and a continuation-in-part of Application No. 07/735,064, filed July 25, 1991 (abandoned). --

IN THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 37-40 and 42-48 are amended, and new claims 49-54 are added.

1-36. (Canceled).

37. (Currently amended) A method of treating a patient having a disease, condition or disorder characterized by an increased number of CD4 positive lymphocytes comprising administering a therapeutically effective amount of a chimeric anti-CD4 antibody that comprises ~~Old World Monkey variable~~ heavy and light chain variable regions of an Old World Monkey antibody and human antibody constant regions, wherein said chimeric antibody inhibits CD4-positive dependent T cell responses.

38. (Currently amended) The method of claim 37 wherein said disease, ~~or~~ condition or disorder is selected from the group consisting of leukemia, lymphoma, asthma, HIV infection, and transplant rejection, and ~~or graft-vs-host~~ graft-versus-host disease.

39. (Currently amended) The method of claim ~~37~~ 38, wherein said disease, ~~or~~ condition or disorder is ~~a non-autoimmune~~ transplant rejection or graft-versus-host disease.

40. (Currently amended) The method of claim 37 wherein said disease, ~~or~~ condition or disorder is an allergic condition.

41. (Previously presented) The method of claim 40 wherein said allergic condition is asthma.

42. (Currently amended) The method of claim 37 wherein said chimeric anti-CD4 antibody has a human antibody gamma 4 constant ~~domain~~ region.

43. (Currently amended) The method of claim 37 wherein said anti-CD4 antibody has a human antibody gamma 1 constant ~~domain~~ region.

44. (Currently amended) The method of claim 42 wherein said gamma 4 constant region ~~domain has the amino acids at position 229 and 236 in the constant region respectively changed from a serine to a proline and a leucine to glutamatic acid~~ comprises at least one mutation selected from the group consisting of:

substitution of glutamic acid in place of leucine at position 248 (Kabat numbering); and

substitution of proline in place of serine at position 241 (Kabat numbering).

45. (Currently amended) The method of claim 37 wherein said Old World Monkey ~~variable~~ heavy and light chain variable regions ~~are~~ have polypeptide sequences encoded by the DNA sequences ~~having~~ in SEQ ID NO.: 3 and SEQ ID NO.: 1 respectively.

46. (Currently amended) The method of claim ~~37~~ 38, wherein said disease, ~~or~~ condition or disorder is lymphoma.

47. (Currently amended) The method of claim 37 wherein said disease, ~~or~~ condition or disorder is an autoimmune or chronic inflammatory disease, condition or disorder.

48. (Currently amended) The method of claim ~~37~~ 47, wherein said autoimmune or chronic inflammatory disease, ~~or~~ condition or disorder is selected from the group consisting of Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type I diabetes mellitus, Goodpasture's syndrome, myasthenia gravis, multiple sclerosis, male infertility, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, inflammatory bowel disease syndrome, Sjögren's syndrome, psoriasis, rheumatoid arthritis, dermatomyositis, scleroderma, mixed tissue connective disease, discoid lupus erythematosus, systemic vasculitis, and systemic lupus erythematosus (SLE).

49. (New) The method of claim 48, wherein the autoimmune or chronic inflammatory disease, condition or disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, type I-diabetes mellitus, cirrhosis, inflammatory bowel disease, SLE, and multiple sclerosis.

50. (New) The method of claim 37, wherein the chimeric anti-CD4 antibody comprises:

a heavy chain having a polypeptide sequence selected from the group consisting of the gamma 4 heavy chain polypeptide sequence in SEQ ID NO:7, the gamma 4 (E) heavy chain polypeptide sequence in SEQ ID NO:9; and the gamma 4 (PE) heavy chain polypeptide sequence in SEQ ID NO:11; and

a light chain having the variable region polypeptide sequence in SEQ ID NO:1 and a constant region polypeptide sequence of a human kappa or lambda light chain.

51. (New) The method of claim 50, wherein the chimeric anti-CD4 antibody comprises a heavy chain having the gamma 4 heavy chain polypeptide sequence in SEQ ID NO:7.

52. (New) The method of claim 50, wherein the chimeric anti-CD4 antibody comprises a heavy chain having the gamma 4 (E) heavy chain polypeptide sequence in SEQ ID NO:9.

53. (New) The method of claim 50, wherein the chimeric anti-CD4 antibody comprises a heavy chain having the gamma 4 (PE) heavy chain polypeptide sequence in SEQ ID NO:11.

54. (New) The method of claim 50, wherein the chimeric anti-CD4 antibody comprises a light chain having the lambda light chain polypeptide sequence in SEQ ID NO:5.

II. REMARKS

Preliminary Remarks

In response to the Notice of Non-Compliant Amendment dated December 9, 2003, the preliminary amendment is re-written so that the amendments of the specification, the amendments of the claims, and the remarks thereon each begin on a separate page.

Claims 37-40 and 42-48 are amended, and new claims 49-54 are added. Claims 37-40, 42-44, and 46-48 are amended to be directed to a method of treating a patient having a disease, condition or disorder characterized by an increased number of CD4 positive lymphocytes, and claims 42-44 are amended to refer to constant and variable regions rather than "domains," so that there is consistency in the language of the independent and dependent claims. Claims 37, 42, and 43 are further amended to more clearly specify that the chimeric anti-CD4 antibody comprises heavy and light chain variable regions of an Old World Monkey antibody and human antibody constant regions. Claim 44 is amended to specify the positions of the E and PE mutations by reference to Kabat numbering, as described on page 26, lines 21-25. These amendments are believed to result in more precise identification of the claimed invention.

Claim 45 is amended to identify the chimeric anti-CD4 antibody in terms of its polypeptide sequence. Amended claims 38, 39, 47 and 48 and new claim 49 are directed to a method of treating a patient having an autoimmune, chronic inflammatory, or non-autoimmune disease, condition or disorder selected from the sets of such diseases, conditions, and disorders disclosed in the specification (*e.g.*, on pages 19-20). New claims 50-54 are directed to the method wherein the chimeric anti-CD4 antibody comprises a light or heavy chain having one of the disclosed polypeptide sequences described in the application. The amended and new claims remain directed to the same classes or genera of disease and antibody type as did the claims prior to this amendment.

Patentability Remarks:

35 U.S.C. § 112, Second Paragraph.

Claim 39 was rejected under 35 U.S.C. § 112, second paragraph, because the term "non-autoimmune" allegedly made the claim indefinite. Claims 38 and 39 are amended to be directed to a method of treating a patient having a disease, condition or disorder that is

selected from the set of non-autoimmune diseases, conditions and disorders described in the specification, for example, on page 20. Withdrawal of the rejection is respectfully requested.

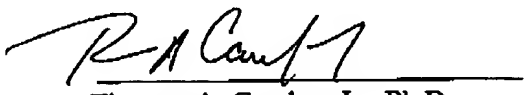
Non-Statutory Obviousness-Type Double Patenting.

Claims 37 and 47 were rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 5,756,096 to Newman et al., which issued from Application No. 08/379,072, for which priority is also claimed by the present application. A terminal disclaimer over Application No. 08/379,072 was filed on July 11, 2003, with the reply to the final office action; in view of which the applicants respectfully request that the obviousness-type double patenting rejection be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,



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